

### **REMARKS/ARGUMENTS**

Reconsideration of this application is requested. This Amendment is responsive to the issues raised in an Office Action dated June 23, 2011, a final rejection, and accompanies a Request for Continued Examination (as well as a 3 month extension of time).

Claims 1, 3-7, 9-11, 13 and 14 will be pending in the application subsequent to entry of this Amendment.

Responsive to paragraphs 1-2 of the Action claims 15 – 32 have been deleted this action taking without disclaimer and without prejudice to a divisional patent application directed to this subject matter.

In paragraph 4 of the Action the Examiner states that certain features of claim 1 are not considered to make a patentable contribution, in other words he does not consider them to be features which limit the scope of the claim, because they are not quantified. This objection applies to the functional limitation that the phase behavior, particle size distribution and/or storage stability are improved in the particles formed by the claimed method.

In paragraph 6 of the Action the Examiner maintains his objection that claim 14 is outside the scope of claim 1. Claim 14 is considered to be inconsistent with the requirements of claim 1, apparently because claim 1 is directed to a method for formation of a dispersion, which requires dispersing particles in a polar solvent followed by heating and cooling to improve the specified properties of the particles, while claim 14 requires the additional step of drying the particles.

In response to this objection, claim 14 is above amended to stipulate that re-suspension/hydration follows the drying of the particles (basis in page 31, lines 13-15 of second paragraph).

In paragraph 10 of the Office Action the Examiner asserts that claims 1, 3-5, 9-11 and 13-14 are anticipated by US 5670099 (Morancais *et al.*). In paragraph 11 the Examiner urges that claims 1-7, 9-11 and 13-14 are obvious in view of the combination of US 6482517 (Anderson I), US 2003/0232340 (Anderson II) and Morancais *et al.* These are largely a repetition of the Examiner's objections in the previous Office Action.

As discussed above, the Examiner has disregarded the requirement that the process results in the formation of particles with improved phase behavior, particle size distribution

and/or storage stability. Current claim 1 requires that the heating is to a suitable temperature for a time sufficient to provide these improvements, stipulating the particular reaction conditions used.

In paragraphs 12 and 13 the Examiner rejects the arguments filed in response to the previous Office Action. The improvements brought about by the method are a key aspect of the invention, not surprising that the Examiner is finding the case obvious if he is ignoring many of the primary contributions made by the inventors. Claim 1 is above amended so that these features are expressed in a way that these features will be taken into account.

The Examiner refers to the definition of the structuring agent in the specification and states that this is characterised as forming lamellar phases, and being amphiphilic. It appears that the Examiner is referring here to the section of the description running from the last paragraph of page 14 to the penultimate paragraph of page 16. The third paragraph of page 16 states that structuring agents are any agents that are capable of forming a *non*-lamellar phase.

The Examiner further states that the characterization of lamellar and non-lamellar phases are not quantified, and lamellar compositions would not be expected to be ideal or thermodynamically stable.

In view of the Examiner's continued objection that lamellar and non-lamellar phases are not "characterized" in the claims, claim 1 is amended to stipulate that non-lamellar particles are particles having an internal region of a normal or reversed cubic or hexagonal phase, or L3 phase, or combination thereof, and further that lamellar particles have a solvent core region (basis in the paragraph bridging pages 11 and 12).

In addition, claim 1 is also amended to include a quantified interpretation of the "improvement in phase properties", by incorporating the subject-matter of claim 2, which specifies a particular conversion rate between lamellar and non-lamellar particles after cooling. The specific phase behavior is further defined by the limitation to a *reversed-phase* non-lamellar core region.

Claim 2 is now redundant and is deleted.

Morancais *et al.* relates to the preparation of submicronic particles in the presence of lipidic vesicles via a dispersion method. Column 10 (lines 20-34) of Morancais *et al.* are

considered to disclose a process having all the features of the process of previous claim 1. This passage refers to the preparation of a lamellar phase by dissolving lipids in a solvent before forming the walls of vesicles, evaporating the solvent, admixing the resulting lipidic combination with an aqueous phase, homogenizing and heating to 10-150 °C (preferably 40-80 °C) for 0.25 hours, followed by cooling to ambient temperature. The homogenization-heating-cooling cycle is repeated at least once. The listed solvents include polar solvents such as alcohols.

Morancais *et al.* specifically refers to formation of a *lamellar* phase, whereas claim 1 refers to the conversion of lamellar phase particles into *reversed phase cubic, hexagonal or L<sub>3</sub> phase* amphiphile particles. Amended claim 1 now explicitly differentiates between lamellar and non-lamellar particles by their structural features and provides a method for converting the former into the latter, as described in the Examples of the application. The lamellar particles of amended claim 1 are characterized in that they have a solvent core region. In contrast, the non-lamellar particles of amended claim 1 have a non-lamellar core region, rather than a solvent core region. Thus the claim comprises explicit definitions of the specific phase structures and requires conversion between them.

Furthermore, the claimed method requires formation of a dispersion of lamellar (or optionally non-lamellar) particles comprising at least one structuring agent. The response to the previous Office Action pointed out that the need for a structuring agent in the current claims, since the Examiner appeared to be either overlooking this or construing the term "structuring agent" so as to include a "lipid capable of forming vesicles".

Finally, and most importantly, the heating-cooling treatment of Morancais *et al.* is part of the process of lamellar phase formation, i.e. it is one stage in the preparation of a dispersion, it is not heat-treatment of a dispersion of particles to alter their phase behavior, as required by the amended claim 1 nor is any method for phase conversion disclosed. Amended claim 1 now requires that the heating provides conversion of at least 50% of lamellar particles to non-lamellar form, after cooling. This is evidently not the case in Morancais *et al.* since that document does not provide any method for converting at least 50% of lamellar particles to non-lamellar phase. Example 1 of Morancais *et al.* makes clear that the homogenization-heating-cooling treatment in stage 2 of the process of Morancais *et al.* results in the formation

of a lamellar phase, which is subsequently treated by stirring/shaking to obtain a dispersion. No heating or phase conversion of this dispersion is provided. It is thus clear that there is no heat treatment of a dispersion of particles disclosed in Morancais *et al.* and thus can be no phase conversion of particles in such a dispersion, as required by amended claim 1.

In view of the distinctions outlined above, it is clear that the amended claims are novel over Morancais *et al.* Moreover, since the Examiner has not raised an anticipation objection against claim 2, it is believed that the novelty of the amended claims is unambiguously established by the incorporation of this subject-matter.

Turning to the Examiner's objections in relation to obviousness, the previous arguments still apply but furthermore the prior art is completely devoid of teaching towards any method for converting lamellar particles in a dispersion to non-lamellar phase.

The Examiner indicates that he considers the claim in which both non-lamellar and lamellar particles are dispersed to be obvious in view of the disclosures of Morancais *et al.* The Examiner considers that the same process is disclosed by Morancais *et al.* and this would be expected to form non-lamellar phases at the phase transition temperature, which would be expected to vary based on the amphiphiles, polar solvent etc. which are used. Morancais *et al.* specifies heating conditions of 10-150 °C for 0.25 hours (15 minutes). The preferred heating temperature is 40-80 °C, thus Morancais *et al.* teaches away from the range of temperatures used in amended claim 1 of the current application. Moreover, as noted above the process of Morancais does not involve heat-treatment of a dispersion of particles, as required by the current invention. There is no discussion of this feature or its possible effects in Morancais *et al.*, which therefore cannot provide any motivation for the skilled worker to develop the current process.

Most significantly, the present invention provides and exemplifies a way in which a dispersion comprising lamellar particles of the specified type can be treated to convert at least 50% of the lamellar particles to non-lamellar form. None of the prior art includes such a conversion step and there is no suggestion in Morancais *et al.* -- or any of the other cited documents -- that any further control over the phase behavior is possible after the dispersion has been formed.

In paragraph 11 of the Office Action the Examiner asserts that claims 1-7, 9-11 and 13-14 are obvious over US 6,482,517 (Anderson I) in view of US 2003/0232340 (Anderson II).

The Examiner considers that the reference to Anderson I disclosing "methods for producing dispersions of coated particles of a wide range of liquid crystalline phases... includ[ing] heating-cooling temperature cycles..." in paragraph [0057] of Anderson II would be enough to make the skilled worker perform the process disclosed in Example 10 of Anderson I, in order to achieve the advantages taught in Anderson II. Applicants disagree.

In Example 10 of Anderson I the dispersion of microparticles is not formed until *after* the heating and cooling steps, in fact after acidification, stirring, shaking and sonication steps which follow the heating and cooling. The current process requires the phase-conversion of a dispersion of particles, which are heated and cooled to achieve phase-conversion *after formation*. It is clear, therefore, that the process disclosed in Anderson I is significantly different from that of the current invention.

Anderson II states that "dispersing cubic and hexagonal phases is... different from dispersing the lamellar phase... sonicating lamellar phase or lamellar phase-forming lipids in water, often does not work with cubic and hexagonal phases..." and "...the present inventor described methods for producing coated particles of a wide range of liquid crystalline phases including cubic and hexagonal. These methods include... heating-cooling temperature cycles... and other methods for solid, typically brittle coating phases, in combination with sonication or other steps for cracking the coated material into coated particles containing liquid crystal.", see paragraph [0057].

The above confirms that the particles produced by the process of Anderson I differ from those of the current invention, and that the processes themselves also differ. Anderson I is directed to forming coated lamellar particles. The current application forms non-lamellar particles, which are explicitly characterized in amended claim 1 with reference to certain phase structures. Anderson I forms a dispersion of particles as the final step in its process, by means of stirring, shaking and sonication. The current process requires formation of a dispersion of particles *prior* to the heating and cooling treatment which produces a phase-conversion.

Furthermore, Anderson II rejects non-lamellar particles (as defined in the current invention), later in paragraph [0057], stating that "...particles of reversed cubic and reversed hexagonal phases with a distinct surface phase comprising a lamellar [or] crystalline lamellar... phase... are not useful *per se* in the instant invention, because they do not allow diffusion of the analyte into the liquid crystal...". Clearly Anderson II teaches away from the process of the present invention.

From the above it will be apparent that the process of Anderson I is not the same as that of the current invention and would not lead to the same products. Anderson II explicitly rejects the particles formed in the process of the current invention in terms of their suitability for the applications of interest in that document. Hence there is no incentive or teaching in Anderson I or Anderson II which could direct the skilled worker to develop the current invention, either alone or in combination. Furthermore, neither document makes any attempt at control over particle phase once in dispersion, nor suggests that this might be possible. There is no reason for the skilled person to contemplate converting at least 50% of lamellar particles to non-lamellar phase on the basis of the teaching of these documents, nor do these documents teach the skilled worker how such particles may be manipulated.

Please also consider the following general comments when assessing the patentability of the amended claims:

It is important to appreciate that the compositions of the present invention are not fully defined by their components. Just as, for example, an emulsion differs in properties from the same two liquids present in two un-mixed layers, so the presence of the particles in the compositions of the present invention, their sizes, size distributions, and internal structures play a key role in defining the properties of the compositions.

Taking this key issue first, it is noted that the Examiner states in paragraph 11 that modifying process conditions such as temperature is not a patentable modification without showing criticality for a result-effective variable. In other words, a difference in the method of the present invention, being the addition of a high temperature step, is not considered to have a technical effect that can be ascribed to this. Such a technical effect is, however,

exhaustively documented in the Examples of the application, and is a key contribution of the present invention.

In the present case, there are two competing issues of thermodynamic and kinetic stability. The thermodynamic form of the individual particles is non-lamellar, but the kinetic barrier is so high that it would take months or years for them to transform into a non-lamellar state under usual storage conditions. Conversely, the non-lamellar particles are generally thermodynamically unstable with respect to conversion into a bulk non-lamellar phase (with a separate solvent phase), corresponding to the separation of an oil-in-water emulsion.

The present inventors have now established that the presence of "contaminant" lamellar particles in the dispersion, and a broad size distribution, tends to cause faster separation of the particles into bulk phases. Unexpectedly, they have found that the heat treatment step described in the present application has the twin effects of bringing essentially all particles into the thermodynamic non-lamellar state, while achieving a non-thermodynamic narrowing of the particle size distribution. The combination of these effects then results in a dispersion which is thermodynamically stable with respect to phase behavior and surprisingly kinetically stable with respect to fusion of the particles and separation into bulk phases.

Attention is invited to Examples 2 and 3 of the present application, in which a dispersion is formed using conventional methods, analyzed for phase behavior, heat-treated and then re-analyzed. In the first analysis (shown in Figure 3), very few of the particles were seen to be non-lamellar, while following the heat treatment step, essentially all had the structure shown in Figure 4. Example 16 and Figures 14 and 16 then show the resultant effect of this structural change: The untreated peak of b) from Fig 14 becomes bi-modal and shifts to larger diameter as peak a) of Fig 16. In contrast, peak b) of Figure 16 is essentially indistinguishable from the corresponding peak (c) of Figure 14. It is thus clear that both the individual particles, and the dispersion as a whole are significantly affected by the heat treatment step.

As further explanation and background to the invention, please see the paper published by the present inventors with regard to the method of the invention (Langmuir **2005**, 2569-2577), which was filed with the response to the previous Office Action. This will be referred to herein as Barauskas *et al.* It must be seen as evident that a method having no technical

effect is unlikely to merit a full paper in such a major international journal, and thus applicants submit that the present method is clearly recognized as making a significant contribution to the relevant art. The issues of stability, particle sizes and phase behavior are also discussed in some detail in this paper.

In view of the above discussion, and in particular in view of Figure 3, which shows directly that particles formed by conventional methods are largely lamellar, it is clear that there is no evidence to suggest any great proportion of these particles of in fact inhabit their thermodynamic state. Certainly, Figure 3 suggests that much less than 50%, and evidently less than 75% do so. Figure 5 of the enclosed document Barauskas *et al.* provides further evidence of this.

Turning to the issue of non-obviousness, the Examiner's dismissal of any technical difference provided by temperature changes serves most clearly to demonstrate that the effects observed by the present inventors were highly unexpected. There is no prior art suggesting that phase behavior, particle size distribution, or particle distribution stability could be affected by heat treatment, and certainly nothing to suggest the positive contribution to all of these factors demonstrated in the Examples and Figures. Applicants reiterate that a nine-page paper in a major international journal is never allocated to processes having no value. There is clearly, therefore, a significant technical contribution made to the art by the methods of the present invention, and there is absolutely no suggestion in the prior art that this could be the case. This contribution is demonstrated in the Examples of the application and further in the experiments described in Barauskas *et al.*

The problem addressed by the present invention is to provide and improve the properties of non-lamellar dispersions. This is achieved, as clearly shown in the Examples of the application and in Barauskas *et al.*, by the heat treatment method claimed. No prior art suggests this method or its benefits, and thus it cannot be seen as obvious. The independent claims of the amended claim set thus all embody an inventive step.

All outstanding issues have been addressed and this application is in condition for allowance. Should any minor issues remain outstanding, the Examiner should contact the undersigned at the telephone number listed below so they can be resolved expeditiously without need of a further written action.



WÖRLE ET AL.  
Appl. No. 10/566,972  
December 23, 2011

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 14-1140.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By: /Arthur R. Crawford/  
Arthur R. Crawford  
Reg. No. 25,327

ARC:caw  
901 North Glebe Road, 11th Floor  
Arlington, VA 22203-1808  
Telephone: (703) 816-4000  
Facsimile: (703) 816-4100